TRANSMITTAL LETTER TO THE UNITED STATES ATTORNEY'S DOCKET NUMBER 0480/01211

DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371 U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP 00/00306	**15 January 2000**	**22 January 1999**

TITLE OF INVENTION: A PROCESS FOR REDUCING THE CONTENT OF ETHYL 3-DIMETHYLAMINO-2-PHENYLPROPIONATE IN SOLUTIONS OF ETHYL 2-DIMETHYLAMINO-1-PHENYL-3-CYCLOHEXENE-1-CARBOXYLATE

APPLICANT(S) FOR DO/EO/US Marco THYES, Wolfgang FALKENBERG, Ulrich SCHNEIDER

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. /X/ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.

2. / / This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.

3. /X/ This express request to begin national examination procedures (35 U.S.C.371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. /x/ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. /X/ A copy of the International Application as filed (35 U.S.C. 371(c)(2)).

   a./X/ is transmitted herewith (required only if not transmitted by the International Bureau).
   b./ / has been transmitted by the International Bureau.
   c./ / is not required, as the application was filed in the United States Receiving Office (RO/US0).

6. /X/ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. / / Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).

   a./ / are transmitted herewith (required only if not transmitted by the International Bureau).
   b./ / have been transmitted by the International Bureau.
   c./ / have not been made; however, the time limit for making such amendments has NOT expired.
   d./ / have not been made and will not be made.

8. / / A translation of the amendments to the claims under PCT Article 19(35 U.S.C. 371(c)(3)).

9. / / An oath or declaration of the inventor(s)(35 U.S.C. 171(c)(4)).

10./ / A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11./x/ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12./ / An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13./x/ A FIRST preliminary amendment.
/ / A SECOND or SUBSEQUENT preliminary amendment.

14./ / A substitute specification.

15./ / A change of power of attorney and/or address letter.

16./x/ Other items or information.
International Search Report
International Preliminary Examination Report

[redacted]

09889383 .020502

09/889383

JC18 Rec'd PCT/PTO 17 JUL 2001

U.S. Appln. No. (If Known)	INTERNATIONAL APPLN. NO. PCT/EP00/00306	ATTORNEY'S DOCKET NO. 0480/01211

17. /X/ The following fees are submitted	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)): Search Report has been prepared by the EPO or JPO.....$860.00	**860.00**	
International preliminary examination fee paid to USPTO (37 CFR 1.482).....$750.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).....$700.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO .....$ 970.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied pro -visions of PCT Article 33(2)-(4).....$96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of $130.00 for furnishing the oath or declaration later than / / 20 / /30 months from the earliest claimed priority date (37 CFR 1.492(e)).		

Claims	Number Filed	Number Extra	Rate	
Total Claims	1	-20	X$18.	
Indep.Claims	1	-3	X$80.	
Multiple dependent claim(s)(if applicable)		+270.		
TOTAL OF ABOVE CALCULATION			= 860.00	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				
SUBTOTAL			= 860.00	
Processing fee of $130. for furnishing the English translation later than / /20 / /30 months from the earliest claimed priority date (37 CFR 1.492(f)).		+		
TOTAL NATIONAL FEE			= **860.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) $40.00 per property		=		
TOTAL FEES ENCLOSED			= **$ 860.00**	
		Amount to be refunded:	$	
		Charged	$	

a./X/ A check in the amount of $ 860. to cover the above fees is enclosed.

b./ / Please charge my Deposit Account No._____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c./X/ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **11-0345**. A duplicate copy of this sheetis enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b) must be filed and granted to restore the application to pending status.

Herbert B Keil
SIGNATURE

SEND ALL CORRESPONDENCE TO:
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Herbert B. Keil
NAME
Registration No. 18,967

[redacted]

09/889383

JC18 Rec'd PCT/PTO 17 JUL 2001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of
THYES et al.

BOX PCT

International Application
PCT/EP 00/00306

Filed: ~~January 27, 2000~~ January 15, 2000

For: A PROCESS FOR REDUCING THE CONTENT OF ETHYL 3-DIMETHYLAMINO-2-PHENYLPROPIONATE IN SOLUTIONS OF ETHYL 2-DIMETHYLAMINO-1-PHENYL-3-CYCLOHEXENE-1-CARBOXYLATE

PRELIMINARY AMENDMENT

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Prior to examination, kindly amend the above-identified application as follows:

IN THE CLAIMS

Kindly amend the claim as shown in the attached sheet.

REMARKS

The sole claim in the case has been amended to put the claim in better form for U.S. filing. No new matter is included.

Favorable action is solicited.

Respectfully submitted,

KEIL & WEINKAUF

/HBKeil

Herbert B. Keil
Reg. No. 18,967

1101 Connecticut Ave., N.W.
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(202)659-0100

CLEAN VERSION OF THE CLAIM - 0480/01211

A process for reducing the content of ethyl 3-dimethylamino-2-phenylpropionate in a solution, contaminated therewith, of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate in a water-immiscible solvent, which comprises adding from 0.5 to 2.0 equivalents of a carboxylic acid per mole of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate to this solution, and stirring this mixture at a temperature of from 50°C to 100°C, wherein the content of 3-dimethylamino-phenyl- propionic acid-ethylester is below 0.10%.

MARKED UP VERSION OF THE CLAIM - 0480/01211

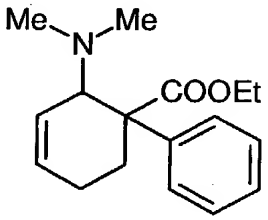
A process for reducing the content of ethyl 3-dimethylamino-2-phenylpropionate in a solution, contaminated therewith, of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate in a water-immiscible solvent, which comprises adding from 0.5 to 2.0 equivalents of a carboxylic acid per mole of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate to this solution, and stirring this mixture at a temperature of from 50°C to 100°C, wherein the content of 3-dimethylamino-phenyl- propionic acid-ethylester is below 0.10%.

A process for reducing the content of ethyl 3-dimethylamino-2-phenylpropionate in solutions of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate

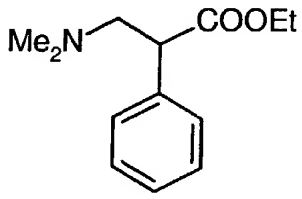
The invention relates to a process for reducing the content of ethyl 3-dimethylamino-2-phenylpropionate (2) in ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate (1), which is a starting material for preparing the analgesic tilidine. Tilidine is the trans isomer of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate and is commercially available as tilidine hydrochloride hemihydrate.

Ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate results as a mixture of cis and trans isomers on reacting ethyl atropate with 1-dimethylaminobutadiene. DE 1 923 620 describes a process for preparing ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate in which it is unnecessary to employ the 1-dimethylaminobutadiene in isolated form for reaction with ethyl atropate; on the contrary, the process entails reacting crotonaldehyde in the presence of potassium carbonate as water-binding agent and of catalytic amounts of a quinone in an inert solvent at from 3 to 5°C with dimethylamine, and reacting the product obtained in this reaction with ethyl atropate to give ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate (mixture of cis and trans isomers).

The synthesis is accompanied by the formation of a second component, ethyl 3-dimethylamino-2-phenylpropionate.



(1)



(2)

Ethyl 3-dimethylamino-2-phenylpropionate is produced in the reaction mixture formally by addition of dimethylamine onto ethyl atropate, the dimethylamine being liberated for example as a consequence of polycondensation of 1-dimethylaminobutadiene or as a consequence of processes of condensation between 1-dimethylaminobutadiene and excess crotonaldehyde.

The extent of the formation of ethyl 3-dimethylamino-2-phenylpropionate depends on the molar ratio of the amounts of ethyl atropate and dimethylamine reacted and is moreover influenced by the nature of the solvent employed [Ann. Chem. 728, 64 (1969)]. The presence of potassium carbonate during the reaction appears to inhibit the formation of ethyl 3-dimethylamino-2-phenylpropionate.

The ethyl 3-dimethylamino-2-phenylpropionate is not removed in the known way (DE 1.923.620) for isolating and purifing ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate (mixture of cis and trans isomers). In the separation of isomers in a known manner (DE 1 923 620, GB 1 226 318), e.g. by selective complex formation with zinc ions or selective salt formation with oxalic acid, which is necessary for isolating tilidine (trans isomer), there is in fact enrichment of the impurity relative to the active substance (DE 1 923 620), with the consequence that, in order to meet the specification of a maximum of 0.10% ethyl 3-dimethylamino-2-phenylpropionate in tilidine hydrochloride hemihydrate, removal must be carried out, for example by recrystallization of the tilidine salt.

It is admittedly stated in DE 1 923 620 that it is possible in principle on preparation of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate by the process described above to achieve an ethyl 3-dimethylamino-2-phenylpropionate content of about 0.1%. However, it has emerged in practice that the content is from 0.3 to 2%.

It is an object of the present invention to provide a simple, low-cost process for reducing the ethyl 3-dimethylamino-2-phenylpropionate content at an early stage of tilidine preparation.

We have found that this object is achieved by a process for reducing the content of ethyl 3-dimethylamino-2-phenylpropionate in a solution, contaminated therewith, of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate in a water-immiscible solvent, which comprises adding from 0.5 to 2.0

equivalents of a carboxylic acid per mole of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate to this solution, and stirring this mixture at a temperature of from 50°C to 100°C.

Suitable water-immiscible solvents are aromatic hyddrocarbons such as toluene, cyclic or acyclic aliphatic hydrocarbons, such as cyclohexane, or aliphatic ethers such as diisopropyl ether. Aromatic and aliphatic carboxylic acids such as formic acid and, preferably, acetic acid are suitable as carboxylic acid. The acid is employed in an amount of from 0.5 to 2.0 equivalents, preferably 0.75 to 1.25 equivalents, per mole of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate.

The mixture obtained in this way is stirred at a temperature of from 50°C to 100°C, preferably 70°C to 90°C, until the ethyl 3-dimethylamino-2-phenylpropionate content reaches a level which can be tolerated for the subsequent preparation process, as a rule for about 0.5 to 2 hours.

After the end of the reaction, the ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate is isolated from the reaction mixture in a conventional way. Thus, the ester can be isolated and purified by adding water to the reaction mixture and making it alkaline. The aqueous phase can then be separated off, and the organic phase can be washed where appropriate with sodium disulfite solution and concentrated.

This results in an ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate which has an ethyl 3-dimethylamino-2-phenylpropionate content below 0.10%.

It is preferred to use for the purification the mixture of cis and trans isomers which is produced initially in the synthesis of the ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate. Virtually no cis/trans isomerization of the ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate is observed on removal of ethyl 3-dimethylamino-2-phenylpropionate by the novel process. This contrasts with the setting up of an isomer equilibrium observed (DE 1 951 587) on heating ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate in glacial acetic acid or aqueous acetic acid. Since virtually no cis/trans isomerization occurs in the novel purification process, it can also be applied in particular to tilidine itself, i.e. to the trans isomer of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate. It is, of course, also possible however for the ethyl

2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate to be in the cis form for the purification.

The novel process is based formally on elimination of dimethylamine from ethyl 3-dimethylamino-2-phenylpropionate. The ethyl atropate formed by the elimination does not interfere with the subsequent process, but can easily be removed by extracting the ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate solution with acid and washing the acid extract with an organic, water-immiscible solvent.

The novel process thus has the advantage of reducing the ethyl 3-dimethylamino-2-phenylpropionate content in the preparation of tilidine so greatly and in a simple, rapid and low-cost way in an early stage of workup that it no longer has interfering effects on the final product.

Example

13.7 g (0.05 mol) of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate (mixture of cis and trans isomers) [ethyl 3-dimethylamino-2-phenylpropionate content (HPLC): 1%], dissolved in 40 ml of cyclohexane, was refluxed with 3.0 g (0.05 mol) of acetic acid for 2 hours. After cooling, 30 ml of water were added. The two-phase mixture was made alkaline with sodium hydroxide solution. The aqueous phase was then separated off. The organic phase was washed with 30 ml of water and concentrated. 13.4 g (98%) of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate isomer mixture of unchanged composition in respect of the cis/trans ratio were obtained with an ethyl 3-dimethylamino-2-phenyl-propionate content of 0.05% (HPLC).

We claim:

A process for reducing the content of ethyl 3-dimethylamino-2-phenylpropionate in a solution, contaminated therewith, of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate in a water-immiscible solvent, which comprises adding from 0.5 to 2.0 equivalents of a carboxylic acid per mole of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate to this solution, and stirring this mixture at a temperature of from 50°C to 100°C.

A process for reducing the content of ethyl 3-dimethylamino-2-phenylpropionate in solutions of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate

Abstract

A process for reducing the content of ethyl 3-dimethylamino-2-phenylpropionate in a solution, contaminated therewith, of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate in a water-immiscible solvent, which comprises adding from 0.5 to 2.0 equivalents of a carboxylic acid per mole of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate to this solution, and stirring this mixture at a temperature of from 50°C to 100°C, is described.

PCT

WELTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales Büro

INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation 7 :
C07C 227/40

A1

(11) Internationale Veröffentlichungsnummer: **WO 00/43353**

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(30) Prioritätsdaten:
199 02 590.8 22. Januar 1999 (22.01.99) DE

(71) Anmelder *(für alle Bestimmungsstaaten ausser US)*: KNOLL AKTIENGESELLSCHAFT [DE/DE]; D–67061 Ludwigshafen (DE).

(72) Erfinder; und
(75) Erfinder/Anmelder *(nur für US)*: THYES, Marco [LU/DE]; Mendelsohnstrasse 31, D–67061 Ludwigshafen (DE). FALKENBERG, Wolfgang [DE/DE]; Nachtigallenweg 12, D–67368 Westheim (DE). SCHNEIDER, Ulrich [DE/DE]; Collingstrasse 63, D–66424 Homburg (DE).

(74) Anwalt: DÖRPER, Thomas; BASF Aktiengesellschaft, D–67056 Ludwigshafen (DE).

(81) Bestimmungsstaaten: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO Patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht
Mit internationalem Recherchenbericht.

(54) Title: METHOD FOR REDUCING 3–DIMETHYLAMINO–2–PHENYLPROPION–ACID ETHYL ESTER–CONTENT IN SOLUTIONS OF 2–DIMETHYLAMINO–1–PHENYL–3–CYCLOHEXENE–1–CARBOXYLIC ACID ETHYL ESTER

(54) Bezeichnung: VERFAHREN ZUR REDUKTION DES 3–DIMETHYLAMINO–2–PHENYLPROPIONSÄURE–ETHYLESTER–GEHALTS IN LÖSUNGEN VON 2–DIMETHYLAMINO –1–PHENYL –3– CYCLOHEXEN–1–CARBONSÄUREETHYLESTER

(57) Abstract

The invention relates to a method for reducing the content of 3–dimethylamino–2–phenylpropionic acid ethyl ester in a solution that is contaminated therewith, whereby the solution is 2–dimethylamino–1–phenyl–3–cyclohexene–1–carboxylic acid ethyl ester, in a solvent which cannot be mixed with water. According to the invention, 0.5 to 2.0 equivalents of a carboxylic acid per mol 2–dimethylamino–1–phenyl–3–cyclohexene–1–carboxylic acid ethyl ester is added to the solution and this mixture is stirred at a temperature of 50 °C to 100 °C.

(57) Zusammenfassung

Es wird ein Verfahren zur Reduktion des Gehalts an 3–Dimethyl–amino–2–phenylpropionsäureethylester in einer hiermit verunreinigten Lösung von 2–Dimethylamino–1–phenyl–3–cyclohexen–1–carbonsäureethylester in einem mit Wasser nicht mischbaren Lösungsmittel beschrieben, welches darin besteht, dass man diese Lösung mit 0,5 bis 2,0 Äquivalenten einer Carbonsäure pro Mol 2–Dimethylamino–1–phenyl–3–cyclohexen–1–carbonsäureethylester versetzt und dieses Gemisch bei einer Temperatur von 50°C bis 100°C rührt.

DECLARATION AND POWER OF ATTORNEY

As a below named inventors, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

A PROCESS FOR REDUCING THE CONTENT OF ETHYL 3-DIMETHYLAMINO-2-PHENYLPROPIONATE IN SOLUTIONS OF ETHYL 2-DIMETHYLAMINO-1-PHENYL-3-CYCLOHEXENE-1-CARBOXYLATE

the specification of which:

[ ] is attached hereto.
[X] was filed on July 17, 2001 as
Application Serial No. 09/889,383
and was amended on _____.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

[ ] In compliance with this duty, attached is an information disclosure statement.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
			Yes	No
199 02 590.6	Germany	1/22/99	[X]	[ ]
			[ ]	[ ]
			[ ]	[ ]
			[ ]	[ ]
Number	Country	Date Filed		

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is

[redacted]

not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

PCT/EP 00/00306	January 15, 2000	Published
Serial No.	Date	Status

I hereby appoint KEIL & WEINKAUF their attorneys and/or agents: Herbert B. Keil, Reg. No. 18,967; Russell E. Weinkauf, Reg. No. 18,495; Gerald H. Bjorge, Reg. No. 32,386; Norman G. Torchin, Reg. No. 34,068; Malcolm J. MacDonald, Reg. No. 40,250; Henry R. Jiles, Reg. No. 32,677; Jason D. Voight, Reg. No. 42,205; George F. Helfrich, Reg. No. 22,350; Ronald H. Smith, Reg. No. 43,679 the address of all being KEIL & WEINKAUF, 1101 Connecticut Avenue, N.W., Suite 620, Washington, D.C. 20036 (telephone (202)659-0100), with full power to prosecute this application and transact all business in the Patent Office connected therewith.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

100

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Full name of sole or first inventor

Marco Thyes — 28.09.01
Inventor's signature — Date

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200

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Ulrich SCHNEIDER
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Inventor's signature

28.9.01
Date

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Citizenship

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Post Office Address

****

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of
THYES et al.

Serial No. 09/889,383

Filed: July 17, 2001

For: A PROCESS FOR REDUCING THE CONTENT OF ETHYL 3-DIMETHYLAMINE-2-PHENYL-PROPIONATE IN SOLUTIONS OF ETHYL 2-DIMETHYLAMINE-1-PHENYL-3-CYCLOHEXENE-1-CARBOXYLATE

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on:

October 3, 2002
Date of Deposit

KAREN STAMPER
Person Making Deposit

Karen Stamper
Signature

October 3, 2002
Date of Signature

Honorable Comm'r. of Patents
Washington, D.C. 20231

CHANGE OF CORRESPONDENCE ADDRESS/
ASSOCIATION WITH CUSTOMER NUMBER REQUEST

Sir:

The office of the attorney of record in this application has moved to the following new address:

Keil & Weinkauf
1350 Connecticut Ave., N.W.
Washington, D.C. 20036
(202) 659-0100

It is further requested that this application be associated with Customer No. 26474 as shown below:

Respectfully submitted,
KEIL & WEINKAUF

HBK/kas

Herbert B. Keil
Reg. No. 18,967

1350 Connecticut Ave., N.W.
Washington, D.C. 20036
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